2017-00187 - Differential model reduction by \((\min,+)\) tropical algebra constraint solving

**Level of qualifications required:** Graduate degree or equivalent
**Fonction:** PhD Position

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### About the research centre or Inria department

The LIFEWARE project-team works in computational systems biology and develops the Biochemical Abstract Machine (BIOCHAM) software for modeling, analyzing and now synthesizing biochemical reaction networks (CRNs) using methods from fundamental computer science and mathematics. The software developments are expected to be integrated in BIOCHAM.

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### Context

This thesis subject is offered at Inria Saclay IdF (https://www.inria.fr/en/centre/saclay) in the LIFEWARE project-team (http://lifeware.inria.fr), in the framework of the ANR-DFG SYMBIONT project on “Symbolic Methods for Biological Networks” (https://www.symbiont-project.org).

The LIFEWARE team works in computational systems biology and develops the Biochemical Abstract Machine (BIOCHAM) software for modeling, analyzing and now synthesizing biochemical reaction networks (CRNs) using methods from fundamental computer science and mathematics. The software developments are expected to be integrated in BIOCHAM.

The thesis will be supervised by François Fages who has supervised 29 Ph.D. theses in his career, the last defended in May 2016, and who currently is 100% available with no Ph.D. student.

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### Assignment

Model reduction is a central topic in differential dynamical systems theory, for reducing the complexity of differential equations, finding important parameters, and developing multi-scale models for instance. While perturbation theory is a standard mathematical tool to analyze the different time scales of a dynamical system, and decompose the system according to fast-slow dynamics, in the domain of computational systems biology, the biochemical reaction networks under consideration involve several time scales of variables which appeal for automated reasoning methods.

Tropicalization is a mathematical method for analysing polynomial equations in the \((\min,+)\) or \((\max,+)\) semiring. The intuitive idea is to reason on the orders of magnitude of concentrations and kinetic parameters which are expressed by the logarithm of their values, hence the \((\min,+)\) algebra for polynomials. We have shown that Constraint Logic Programming can be used to efficiently solve tropical equation problems for identifying the dominating monomials and reactions in a network, and then simplifying the dynamics in the different regions of the phase space corresponding to different regimes (i.e. Quasi Steady State or Quasi Equilibrium assumptions).

The goal of this Thesis, in collaboration with our partners of the ANR-DFG project SYMBIONT, is to generalize our tropical equation solver based on constraint programming to new stability constraints, and to develop the model reduction method by searching for precise approximation results (e.g. using Tikhonov theorem) at least in simple examples like the Michaelis-Menten enzymatic reaction. The method will be implemented in our modeling environment Biocham, evaluated on mcell systems biology models from BioModels repository, and compared to other symbolic methods developed in SYMBIONT.

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### Main activities

Our first results on this subject have been published in

The planned work will consist in:

- generalizing the CLP solver to handle inequalities instead of equalities, with accurate translation from polynomials to (min,+ ) intervals,
- developing correctness criteria for the simplified system (e.g. stability conditions of Tikhonov theorem)
- implementing the model reduction method and evaluating it on models from the BioModels repository.

Further reading:


**Skills**

This subject requires common and basic knowledge on differential equations, linear algebra, algorithms and programming.

There is no specific prerequisite for this internship. However, some specific knowledge on either the algebra (max,+), constraint programming, control theory, or computational systems biology will be a plus.

**Benefits package**

- Subsidised catering service
- Partially-reimbursed public transport
- Social security
- Paid leave
- Flexible working hours
- Sports facilities

**Remuneration**

Monthly gross salary: 1.982 euros (1st and 2nd year) - 2.085 euros (3rd year)